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EXAMINER
GODDARD, LAURA B

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,616	VANDE WOUDE ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,7-18,20-22,26,28-34,37,38 and 40-46* is/are pending in the application.

4a) Of the above claim(s) *9,10,13,16-18,22,26,28-34,37,38 and 40-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7,8,11,12,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/07, 5/22/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Given the confusing nature of the prior restriction requirements, the prior restriction requirements are hereby withdrawn and a new restriction requirement is set forth below.

Restriction is required under 35 U.S.C. 121 and 372.

2. This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1, 5, 7-13, 16-18, 20, and 21, drawn to the special technical feature of a method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of (a) one or more of thrombospondin-1 (TSP-1), an anti-angiogenic derivative thereof, or a TSP-1 agonist or mimic; and in combination with (b) one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; or (iii) both (i) and (ii), thereby inhibiting said angiogenesis.

Group II, claim(s) 22, 26, 28-34, 37, 38, 40-46, drawn to the special technical feature of a composition comprising (a) one or more of TSP-1, an anti-angiogenic derivative

thereof, or a TSP-1 agonist or mimic; and in combination with (b) one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met: (ii) VEGF or the VEGF receptor, or (iii) both (i) and (ii).

3. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking Groups I and II appears to be TSP-1 and an inhibitor of VEGF.

However, said technical feature does not constitute a special technical feature in view US Patent 7,351,729, Stein et al, filed March 7, 2003, issued April 1, 2008, and claiming priority to March 8, 2002. Stein et al teach one or more angiogenesis inhibitors including anti-VEGF antibody bevacizumab and TSP-1, as well as a method of treating cancer in a patient comprising administering bevacizumab and TSP-1 (col. 56, line 1 to col. 58, line 8; col. 58, lines 16-41).

Therefore, the technical feature linking the inventions of Groups I and II does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Accordingly, Groups I and II are not so linked by the same or a corresponding special technical feature as to form a single general incentive concept and restriction for examination purposes as indicated is proper.

SPECIES ELECTION

Species Election for Group I

4. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of methods are as follows:

(a) administering TSP-1 or and TSP-1 agonist in combination with one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; or (iii) both (i) and (ii); or

(b) administering one of more inhibitors that target the MAPK pathway and (i) inhibit upregulation of expression or angiogenic activity of VEGF; (ii) inhibit down-regulation of TSP-1; or (iii) both (i) and

(ii).

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each method requires a different combination of method steps.

5. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of TSP-1 are as follows (claim 1, part a):

(a) TSP-1 or anti-angiogenic derivative, or

(b) TSP-1 agonist or mimic.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each agent is structurally and functionally distinct.

6. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of inhibitor of action or expression (claim 1, part b):

(a) HGF/SF,

(b) HGF/SF receptor Met,

(c) VEGF, or

(d) VEGF receptor.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each protein is structurally and functionally distinct requiring a different inhibitor.

7. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of VEGF inhibitor (claim 7):

(a) anti-VEGF antibody,

(b) anti-VEGF receptor (VEGFR) antibody,

(c) decoy VEGF receptor,

(d) VEGF-Trap,

(e) siRNA for VEGF,

(f) siRNA for VEGFR, or

(g) peptidomimetic inhibitor of VEGFR activation.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each inhibitor is structurally and functionally distinct.

If Applicants elect the species of "(b) administering one of more inhibitors that target the MAPK pathway and (i) inhibit upregulation of expression or angiogenic activity of VEGF; (ii) inhibit down-regulation of TSP-1; or (iii) both (i) and (ii)" in section 4 above, Applicants must elect a species in section 8 below:

8. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species of MAPK inhibitor (claim 13, 16, 17, 18, 20, 21):

(a) MEK inhibitor anthrax lethal factor,

(b) another MEK protease, or

(c) small organic molecule.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: Each inhibitor is structurally and functionally distinct.

9. Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims

are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

10. During a telephone conversation with Mr. Douglas H. Siegel on January 6, 2010 a provisional election was made to prosecute the invention of Group I, claims 1, 5, 7-13, 16-18, 20, and 21, and the species of "(a) administering TSP-1 or and TSP-1 agonist in combination with one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; or (iii) both (i) and (ii)" (section 4 above), "TSP-1" (section 5), "inhibitor of VEGF" (section 6), and VEGF inhibitor "anti-VEGF antibody" (section 7). **Affirmation of this election must be made by applicant in replying to this Office Action.**

11. Because Applicant did not distinctly and specifically point out any errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). Claims 1, 5, 7-18, 20-22, 26, 28-34, 37, 38, and 40-46 are pending. Claims 22, 26, 28-34, 37, 38, 40-46 have been withdrawn from further consideration by the examiner under 35 CFR 1.142(b) as being drawn to non-elected inventions. Claims 9, 10, 13, 16, 17, and 18 are withdrawn as being drawn to non-elected species. Claims 1, 5, 7, 8, 11, 12, 20, and 21 are currently under prosecution as drawn to the elected species.

12. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

13. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during

prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 8 contains the trademark/trade name **Avastin** ®. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe two specific drugs and a specific cream, accordingly, the identification/description is indefinite, MPEP 706.03(d). Amendment, for example, to recite the monoclonal antibody in the product, **bevacizumab**, would obviate the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1, 5, 7, 8, 11, 12, 20, and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent 7,351,729, Stein et al, filed march 7, 2003, issued April 1, 2008, and claiming priority to March 8, 2002, as evidenced by Burke et al (Critical Reviews in Oncology Hematology, 2001, 39:155-171).

The claims are drawn to a method of inhibiting tumor angiogenesis comprising providing to cells that undergo angiogenesis or participate in angiogenesis, an effective amount or amounts of (a) one or more of thrombospondin-1 (TSP-1), an anti-angiogenic derivative thereof, or a TSP-1 agonist or mimic; and in combination with (b) one or more inhibitors of the action or expression of (i) HGF/SF or the HGF/SF receptor Met, (ii) VEGF or the VEGF receptor; or (iii) both (i) and (ii), thereby inhibiting said angiogenesis (claim 1), the method of claim 1, wherein the inhibitor is a VEGF inhibitor (claim 5), the method of claim 5 wherein the VEGF inhibitor is an anti-VEGF antibody (claim 7), the method of claim 7 wherein the VEGF inhibitor is the anti-VEGF monoclonal antibody termed Avastin® (claim 8), the method of claim 1 or 20 wherein said providing is to a subject in vivo, which subject is susceptible to, or at risk of, tumor growth or metastasis,

or in which subject said tumor growth or metastasis is ongoing (claim 11, 12), the method of claim 1 which comprises providing effective amounts of: TSP-1 in combination with an anti-VEGF antibody (claim 20), the method of claim 20 which comprises providing effective amounts of one or more of: (A) TSP-1, (B) an anti-VEGF antibody (claim 21).

Stein et al teach a method of treating cancer in a patient, including several different solid tumors (col. 56, line 1 to col. 58, line 8) comprising administering one or more angiogenesis inhibitors including anti-VEGF antibody bevacizumab and TSP-1 (col. 58, lines 16-41).

As evidenced by Burke et al, angiogenesis, or the growth of blood vessels, is essential for the growth of a primary tumor and for successful metastasis (abstract) and angiogenesis requires endothelial cell activation, proliferation and migration to form tumor vasculature (p. 157, col. 2), hence the administration of bevacizumab and TSP-1 to cancer patients with tumors would necessarily provide bevacizumab and TSP-1 to cells that undergo angiogenesis or participate in angiogenesis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1, 5, 7, 8, 11, 12, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosen (Cancer Control, March/April 2002, 9:36-44) in view of US Patent 7,223,731, Lawler, filed May 2001, issued May 2007, Streit et al (American J of Pathology, 1999, 155: 441-452, IDS), and Burke et al (Critical Reviews in Oncology Hematology, 2001, 39:155-171).

The claims are set forth above.

Rosen teach a method of treating cancer patients and metastatic cancer patients comprising administering anti-VEGF antibody bevacizumab, a known angiogenesis inhibitor (p. 41, col. 2). Rosen teach that VEGF is known as a pro-angiogenic factor and TSP-1 is known as an anti-angiogenic factor (Table 1). Rosen teach that neovascularization is essential for the growth of tumors and metastasis (p. 37, col. 1), and angiogenesis requires endothelial cell proliferation, differentiation and migration (p. 42, col. 1), hence the administration of bevacizumab to cancer patients with tumors would necessarily provide bevacizumab to cells that undergo angiogenesis or participate in angiogenesis.

Rosen does not teach adding TSP-1 to the method of treating cancer.

Lawler teaches TSP-1 is a known potent inhibitor of tumor growth and angiogenesis (abstract). Lawler teaches methods of successfully treating cancer *in vivo* comprising administering TSP-1 peptides (Example 2).

Streit et al also teach that TSP-1 is a potent inhibitor of angiogenesis and tumor growth (abstract; p. 442, col. 1, first paragraph) and demonstrateTSP-1 gene

transfection of tumor cells reduced tumor growth and angiogenesis *in vivo* (Figure 2C-F).

Burke et al teach angiogenesis is required for the growth of tumors and metastasis (abstract) and suggest combining antiangiogenic agents with each other to target more than one mechanism of angiogenesis and produce synergistic combination therapy (abstract; p. 156, col. 1-2; Table 2). Burke et al also teach RhuMAb VEGF (also known as bevacizumab) is a known antiangiogenic agent (Table 1; p. 159, col. 2).

The references suggest the importance of bevacizumab and TSP-1 in cancer and antiangiogenic treatment. However, the references are deficient in that they do not teach using these agents together. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use bevacizumab taught by Rosen and TSP-1 agent taught by Lawler and Streit et al in combination in order to treat cancer and inhibit angiogenesis. One of ordinary skill in the art would have been motivated to use bevacizumab and TSP-1 in combination in a method of treating cancer in view of the importance of inhibiting angiogenesis that contributes to tumor growth. Each of these agents had been taught by the prior art to be effective in the inhibition of angiogenesis and tumor growth, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the

instant process claims and composition claim, given the teaching of the prior art of processes using either bevacizumab or TSP-1 in the process of treating cancer and inhibiting angiogenesis, it would have been obvious to treat cancer with both bevacizumab and TSP-1 because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for the same purpose of treating cancer by inhibiting angiogenesis. Further, one would have been motivated to combine bevacizumab and TSP-1 as antiangiogenic agents for therapy because Burke et al suggest combining antiangiogenic agents with each other to target more than one mechanism of angiogenesis and produce synergistic combination therapy. One of ordinary skill in the art would have reasonably expected to obtain effective treatment of cancer and inhibition of angiogenesis with either or both of these agents since both had been demonstrated in the prior art to successfully treat cancer by inhibiting angiogenesis.

17. **Conclusion:** No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard/
Primary Examiner, Art Unit 1642